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EXAMINER	
ARCHIE, NINA	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPDOCKET@THOMPSONCOBURN.COM

Office Action Summary	Application No.	Applicant(s)	
	10/511,616	CURTISS, ROY	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/3/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-12,14-17,19,21-26 and 31-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed on 8-3-2009. Claims 1, 12, 19, 21, 23, and 31-33 have been amended. Claims 27-30 have been cancelled.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Drawings

3. The drawings filed on date 10/15/2004 in the present application has been stated. However, new corrected drawings are required in this application because the figures are not clear and Examiner is unable to interpret (see 5/54, 6/54, and 7/54). The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Information Disclosure Statement

5. The information disclosure statement filed on 10/7/2007 has been considered. An initialed copy is enclosed.

Election/Restrictions

6. Applicant's election with traverse of Group I claims 1 and 8-10 is acknowledged. The traversal is on the ground(s) below: First Point: the Office's description of claims 1 and 8-10, and claims 2-7 and 33, is verbatim the same and drawn to the same subject matter, therefore, Applicant can find no rationale supporting restriction between claims 1 and 8-10 and claims 2-7 and 33. Furthermore, Applicants state claims 11 and 17 respectively are method claims that use the live attenuated derivative claimed in claim 1 and therefore incorporate by reference to claim

1 all of the limitations including the special technical feature of claim 1. Second Point: Applicant notes that claim 26 has not been designated within one of the ten groups of inventions and that claim 26 is a dependent claim drawn to the same live attenuated derivative of claim 1 and contains all of the limitations of claim 1, therefore, because claim 26 is drawn to the same invention of claim 1. Third Point: Applicants argue Simpson et al merely discloses Staphylococcus aureus fur genes and fails to disclose any of the other features of the invention as claimed. Curtiss et al 2001 describes a very distinct use of the araCPBAD promoter to drive expression of a repressor protein that controls replication of an exogenously provided recombinant DNA vector. In contrast, the araCPBAD promoter is used in the instant application to drive the expression of the fur or other regulatory genes that control various endogenous bacterial genes. The instant invention does not entail use of fur to regulate an exogenously provided recombinant DNA vector. Fourth Point: Applicants argue the relevance of this section of the MPEP to claims that are not nucleotide sequence claims is unclear, particularly where the species identified by the Office Action include carbohydrates and that many of the claims to which this gene election requirement is directed are Markush claims (i.e. claims 3, 36, 37, and 38) where sections of the law outlined in MPEP § 803.02 are pertinent, more specifically, the fliC and fljB mutants of claim 3 are related both structurally and functionally in that they encode mutant flagella as described on page 13 of the specification as filed. Furthermore, search and examination of the two members of claim 3 can be made without serious burden. Fifth Point: Applicants state that the feature of the fur gene being expressed when the attenuated strain is in the intestinal tract of an individual and the gene not being expressed when the attenuated strain is within internal tissues is also a special technical feature common to all the claims, therefore Applicant respectfully contends that the Office has misrepresented the technical features of the claims. This feature is thus a "special technical feature" that provides a common technical relationship among all of the currently pending claims for purposes of unity of invention. (PCT Rule 13.2).

This is not found persuasive because, in regards to First Point: the Examiner has put forward the publications of Simpson et al (US Patent 6,521,441 US Publication Date February 18, 2003 US filing Date January 15, 2002) and Curtiss et al (WO 2001/83785A2 November 8, 2001) as evidenced by Curtiss et al et al (WO1991/006317 Date May 16, 1991), in support of the

belief that claims 1 and 8-10 and the following claims 2-7 and 33 are separate inventions, wherein the restriction for claims 1 and 8-10 and the following claims 2-7 and 33 therefore said inventions are distinct and requires independent searches. In regards to method claims 11 and 17 that use the live attenuated derivative claimed in claim 1, said method claims are distinct from claims 1 and 8-10 and furthermore would require an independent search. In regards to Second Point: a typographical error was made and claim 26 is presently rejoined with claims 1 and 8-10. In regards to Third Point: one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant cannot argue limitations stated in the specification that are not in the instant claims. In regards to Fourth Point: although applicants nonetheless provisionally elects with traverse fliC, (gmd-fcl)-26 (claim 36), and gmd (claim 37), the nucleotide election is based on a specific gene or combination thereof if applicable to the elected Group. Furthermore claims 1 and 8-10 were elected and there is no gene or combination thereof election needed for the elected claims. In regards to Fifth Point: the lack of unity dated on 6/1/09 is based on the claims filed on 2/9/2009. Furthermore, the special technical feature of claims 1 and 8-10 is regarding the mutation of a fur gene within a *Salmonella* species in order to get a regulatable expression. The special technical feature does not make a contribution over the prior art as noted in Simpson et al (US Patent 6,521,441) Curtiss et al (WO 2001/83785A2) as evidenced by Curtiss et al et al WO 1991/006317 Date May 16, 1991. Therefore, unity of invention is lacking. Furthermore, the instant claims 1, 5-6, 8-10, 26 and 31-32 have been rejoined being dependent from claim 1 having the special technical feature of linking various groups with the mutation of various genes within a *Salmonella* species in order to get a regulatable expression.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-6, 8-12, 14-17, 19, 21-26, and 31-40 are pending. Claims 1, 5-6, 8-10, 26, and 31-32 are under examination. Claims 2-4, 14-17, 19, 21-25, 33-40 are withdrawn from consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected (claims 2-4 and 33), (claim 11), (claims 12, 14-16, 19, 21-22 and 33), (claims 23-25), (claims 34-37), (claims 38-39), (claim 40), and (claim 17), there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The claims are drawn to a live attenuated derivative of a pathogenic *Salmonella* species comprising (a) a means for regulatable expression of a fur gene that encodes a regulatory protein, wherein a regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said regulatory protein in vivo causes synthesis of a first antigen that is conserved among *Salmonella* species and *Escherichia* coli (*E. coli)* strains; and (b) a means for regulatable synthesis of a first carbohydrate antigen, wherein said first carbohydrate antigen ceases to be synthesized in vivo, exposing a second carbohydrate antigen that is conserved among *Salmonella* species and *E. coli* strains; wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains (claim 1), wherein said means of regulatable expression comprises substituting the promoter of said gene that encodes a regulatory protein with a regulatable promoter (claim 5), wherein said regulatable promoter is the araCP$_{BAD}$repressor-activator-promoter system (claim 6), wherein said carbohydrate antigen is an LPS O-antigen (claim 8), wherein said means for regulatable synthesis comprises a mutation in a gene that encodes that encodes a product necessary for synthesis of LPS O-antigen (claim 9), wherein said means fore regulatable synthesis comprises a mutation in the pmi gene (claim 10), wherein said pathogenic *Salmonella species* is a *Salmonella typhimurium* comprising (a) a ΔPfur::TTaraCP$_{BAD}$*fur* deletion-insertion mutation; and (b) a Δpmi mutation (claim 26), further comprising a Δpmi mutation (claim 31), consisting of a ΔPfur::TTaraCP$_{BAD}$*fur* genetic construction (claim 32).

Written Description

8. Claims 1, 5-6, 8-10, 26, and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter,

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a vast genus of regulators. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

Applicants must adequately describe the genus of regulators capable non-expression of a regulatory protein in vivo causes synthesis of a first antigen that is conserved among *Salmonella species and Escherichia coli (E. coli)*. Furthermore Applicants must also adequately describe the genus of regulators capable a means of regulating synthesis for a first carbohydrate, wherein said first carbohydrate antigen ceases to be synthesized in vivo, and exposing a second carbohydrate antigen.

Applicants have only disclosed the following. The specification discloses bacterial strains that produce the group B LPS O-antigen side chains using slide agglutination assays within antisera resulting in moderate and high agglutination (see Table 4 pg. 33). The specification discloses a *Salmonella typhimurium* (*S. typhimurium)* strain χ8650 which demonstrates a function of time or number of generations of growth in nutrient broth medium in the absence of added mannose is a gradual loss of LPS O-antigen side chains (see pg. 33 second paragraph). Applicants disclose the administration of the *S. typhimurium* strain χ8650 to mice and further observe the morbidity and mortality for 30 days, wherein the survivors from said strain were challenged with virulent wild-type *S. typhimurium UK-1* χ3761 strain (see pg. 37), wherein the *S. typhimurium* strain χ8650 is grown in a nutrient broth medium in the absence of added

mannose which indicates a gradual loss of LPS O-antigen side chains that are reproduced *in vivo* in said strain after immunization of an animal host, enters visceral tissue. Applicants have disclosed the administration of *S. typhimurium* χ8754 strain and further challenge with virulent wild-type *Salmonella enteritidis* χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to *Salmonella and Escherichia coli (E. coli)* outer membrane proteins *(OMPs)* and iron-regulated outer membrane proteins *(IROMPs)* (see pgs. 41-42). Therefore the specification is limited to *OMP and IROMP* antigens conserved among *Salmonella species and E. coli* strains that are capable of being synthesized caused by non-expression of an iron regulatory protein from fur gene *in vivo* and limited to LPS-O antigens conserved among *Salmonella species and E. coli* strains capable of ceasing synthesis *in vivo*.

Although the specification discloses examples of antigens and carbohydrate antigens regulated, the specification does not teach any structural limitations of any regulators and the specification is silent to the correlation of the genus of regulators and its recited function. The specification fails to disclose how to determine what constitutes a regulator capable non-expression of a regulatory protein in *vivo* causes synthesis of a first antigen that is conserved among *Salmonella species and Escherichia coli (E. coli)*; and what constititues a regulator capable of a means of regulating synthesis for a first carbohydrate, wherein said first carbohydrate antigen ceases to be synthesized in *vivo*, and exposing a second carbohydrate antigen. Furthermore the specification fails to disclose how to determine what constitutes first carbohydrate antigen capable of ceasing synthesis *in vivo* and exposing a second carbohydrate antigen. Therefore, the specification lacks written description of the instant claimed invention. This issue is best resolved by Applicants pointing to the specification by page and line number where description of the claimed invention is set forth.

The limited number of species disclosed in the specification is not deemed to be representative of the genus of regulators encompassed by the instant claims. Moreover, Applicant is reminded that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. Therefore, although the specification discloses examples of antigens and

carbohydrate antigens being regulated, the specification is silent to a core structure of a regulator, and furthermore silent to the correlation of the genus of regulators and its recited function.

The specification, does not disclose distinguishing and identifying features of a representative member of the genus of regulators as to which the claims are drawn, such as a correlation between the structure of regulators and its recited function capable of nonexpression of regulatory protein in vivo causing synthesis of a first antigen that is conserved among *Salmonella species and Escherichia coli (E. coli)* and the capability of a means of regulating synthesis for a first carbohydrate, wherein said first carbohydrate antigen ceases to be synthesized in vivo, and exposing a second carbohydrate antigen, so that the skilled artisan could immediately envision or recognize at least a substantial number of members of the claimed genus of regulators. Moreover, Applicant has not demonstrated any of regulatory protein (regulator) capable of causing synthesis of a first antigen that is conserved among *Salmonella species and E. coli* strains. Moreover, Applicant has not demonstrated any of regulatory protein (regulator) capable of ceasing synthesis *in vivo* and exposing a second carbohydrate antigen that is conserved among *Salmonella species and E. coli* strains. Therefore, the specification lacks written description of the instant claimed invention. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of regulators as to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus aforementioned above.

MPEP § 2163.02 states, "an objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Ink's. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

Therefore, absent a detailed and particular description of a representative number of the members of the genus of regulators, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of regulators with the recited activities. Therefore, in accordance with the *Guidelines*, the description of any regulator is not deemed representative of the genus of regulators to which the claims refer and therefore the claimed invention is not properly disclosed.

Enablement

9. Claim 1, 5-6, 8-10, 26, and 31-32 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Salmonella typhimurium* ΔPfur223::TTaraCP$_{BAD}$*fur* Δpmi-2426 strain comprising (a) a means for regulatable expression of a fur gene that encodes an iron regulatory protein, wherein said araCP$_{BAD}$ regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said iron regulatory protein *in vivo* causes synthesis of an antigen of outer membrane protein (OMP) or iron outer membrane protein (IROMP) that is conserved among *Salmonella* species and E. coli strains, wherein said strain enhances the survival of an infection against *Salmonella* species and *E. coli* strains does not provide enablement for a live attenuated derivative of a pathogenic *Salmonella* species comprising (a) a means for regulatable expression of a fur gene that encodes a regulatory protein, wherein a regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said regulatory protein in vivo causes synthesis of a first antigen that is conserved among *Salmonella* species and *E. coli* strains; and (b) a means for regulatable synthesis of a first carbohydrate antigen, wherein said first carbohydrate antigen ceases to be synthesized in vivo, exposing a second carbohydrate antigen that is conserved among *Salmonella*

species and *E. coli* strains; wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

(A) The nature of the invention;

(B) The breadth of the claims;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention

The instant claims are drawn to a live attenuated derivative of a pathogenic *Salmonella* species comprising (a) a means for regulatable expression of a fur gene that encodes a regulatory protein, wherein a regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non- expression of said regulatory protein in vivo causes synthesis of a first antigen that is conserved among *Salmonella* species and *E. coli* strains; and (b) a means for regulatable synthesis of a first carbohydrate antigen, wherein said first carbohydrate antigen ceases to be synthesized in vivo, exposing a second carbohydrate antigen that is conserved among *Salmonella* species and *E. coli* strains; wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains.

Breadth of the claims

The claims are overly broad. The claims encompass any live attenuated derivative of any pathogenic *Salmonella* species comprising (a) a means for regulatable expression of a fur gene that encodes a regulatory protein, wherein a regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said regulatory protein in vivo causes synthesis of any antigen that is conserved among *Salmonella* species and *E. coli* strains; and (b) a means for regulatable synthesis of any carbohydrate antigen, wherein said carbohydrate antigen ceases to be synthesized in vivo, exposing any carbohydrate antigen that is conserved among *Salmonella* species and E. coli strains, wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against any *Salmonella* species and *E. coli* strains.

Guidance of the specification/The existence of working examples:

Applicants have only disclosed the following. The specification discloses bacterial strains that produce the group B LPS O-antigen side chains using slide agglutination assays within antisera resulting in moderate and high agglutination (see Table 4 pg. 33). The specification discloses a *Salmonella typhimurium* (*S. typhimurium)* strain χ8650 which demonstrates a function of time or number of generations of growth in nutrient broth medium in the absence of added mannose is a gradual loss of LPS O-antigen side chains (see pg. 33 second paragraph). Applicants disclose the administration of the *S. typhimurium* strain χ8650 to mice and further observe the morbidity and mortality for 30 days, wherein the survivors from said strain were challenged with virulent wild-type *S. typhimurium UK-1* χ3761 strain (see pg. 37), wherein the *S. typhimurium* strain χ8650 is grown in a nutrient broth medium in the absence of added mannose which indicates a gradual loss of LPS O-antigen side chains that are reproduced *in vivo* in said strain after immunization of an animal host, enters visceral tissue. Applicants have disclosed the administration of *S. typhimurium* χ8754 strain and further challenge with virulent wild-type *Salmonella enteritidis* χ3700 strain (see pgs. 40-42), wherein the survivors from the challenge induced IgG antibodies to *Salmonella and Escherichia coli (E. coli) OMPs and IROMPs* (see pgs. 41-42). Therefore the specification is limited the survival of mice through the

administration of *Salmonella typhimurium* ΔPfur223::TTaraCP$_{BAD}$*fur* Δpmi-2426 strain. The claimed invention is drawn to cross-protective immunity against *Salmonella* species *and E. coli* strains and as a result cross-protective immunity is correlated to a vaccine. A vaccine by definition must provide protection against an infection demonstrable by challenge experiments. The data as set forth supra does not demonstrate that the live attenuated derivative aforementioned above confers "protection" against infection by *Salmonella* species *and E. coli* strains. The data merely shows that said derivative increases the number of mice that survived from *Salmonella and E. coli* infection. Therefore the data fails to show or vaccine protection against *Salmonella* species *and E. coli* strains. Therefore, one skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of a successful model. The working examples do not disclose any empirical data or results indicative of a preventing *Salmonella and E. coli* infection as claimed. The specification is devoid of any teaching that the claimed prevents *Salmonella and E. coli* infection.

State of the art

The art discloses turkeys passively immunized with antibody against IROMPs of *E. coli* which significantly reduced the growth of bacteremia and the recovery of *E. coli* from air sacs thus increasing the survival of turkeys (see abstract and pg. 1242 specifically and Bolin et al 1987 Infection and Immunity pgs. 1239-1242 in its entirety). The art discloses mice passively immunized with antibody against IROMPs of *Salmonella enterica serovar Typhi* which significantly reduced the growth of bacteremia and increase the survival of mice and indicates that anti IROMPs antibodies may play an important role in providing protection at a systemic and mucosal level (see abstract and pgs. 69-71 and pg. 74 and Sood et al 2005 Molecular and Cellular Biochemistry Vol. 273 pgs. 69-78 in its entirety). Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrasekhar et al., US Patent 6,248,329, col. 1, and lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, et al. (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the

problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.., and thus protect the host against attack by the pathogen." As evidenced by Greenspan et al. (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. For the reasons set forth supra, the state of the art is has limitations to said derivative aforementioned above and the state of the art is unpredictable with regard to said derivative with enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains.

In conclusion, the claimed invention is not enabled for a live attenuated derivative of a pathogenic *Salmonella* species comprising (a) a means for regulatable expression of a fur gene that encodes a regulatory protein, wherein a regulatable promoter is operably linked to said gene, wherein said gene is expressed when said attenuated strain is in the intestinal tract of an individual and said gene is not expressed when said attenuated strain is within internal tissues of an individual and wherein non-expression of said regulatory protein in vivo causes synthesis of a first antigen that is conserved among *Salmonella* species and E. coli strains; and (b) a means for regulatable synthesis of a first carbohydrate antigen, wherein said first carbohydrate antigen ceases to be synthesized in vivo, exposing a second carbohydrate antigen that is conserved among *Salmonella* species and E. coli strains; wherein said attenuated derivative has enhanced ability to induce cross-protective immunity against *Salmonella* species and E. coli strains. Furthermore, the claims encompassing any live attenuated derivative of any pathogenic *Salmonella* species comprising any first antigen and any carbohydrate antigen which has enhanced ability to induce cross-protective immunity against *Salmonella* species and *E. coli* strains is overly broad. The specification fails to teach that said derivative as set forth can

produce a protective response in a host, for prevention of *Salmonella* and *E. coli* as is requisite of a vaccine. The state of the art teaches that there are limitations to a vaccine and the state of the art is unpredictable. In view of the lack of support in the art and specification for an effective vaccine, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed composition.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 5-6, 8-10, 26, and 31-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) As to independent claim 1, and all dependent claims 5-6, 8-10, 26, and 31-32, regarding the word "means" is preceded by the word(s) "means for regulatable" in an attempt to use a "means" clause to recite a claim element as a means for performing a specified function. However, since no function is specified by the word(s) preceding "means," it is impossible to determine the equivalents of the element, as required by 35 U.S.C. 112, sixth paragraph. See *Ex parte Klumb*, 159 USPQ 694 (Bd. App. 1967).

b) As to independent claim 1, and all dependent claims 5-6, 8-10, 26, and 31-32, reciting the phrases "first antigen", "first carbohydrate antigen" "second carbohydrate antigen". However, neither the claim nor the specification clearly defines nor sets forth the meaning or means to assess "first antigen", "first carbohydrate antigen" "second carbohydrate antigen". Therefore, the skilled artisan would not be readily apprised of the metes and bounds of "first antigen", "first carbohydrate antigen" "second carbohydrate antigen" nor how to assess such.

c) As to independent claim 1, and all dependent claims 5-6, 8-10, 26, and 31-32, reciting the phrase "ceases". However, neither the claim nor the specification clearly defines nor sets forth the meaning or means to assess "ceases". Therefore, the skilled artisan would not be readily

apprised of the metes and bounds of "ceases" nor how to assess such. Amendment of the claims to add the word "inhibits" would make the claims clear and obviate this issue.

d) As to independent claim 1, and all dependent claims 5-6, 8-10, 26, and 31-32, reciting the phrase "live attenuated derivative". However, neither the claim nor the specification clearly defines nor sets forth the meaning or means to assess "live attenuated derivative". Therefore, the skilled artisan would not be readily apprised of the metes and bounds of "live attenuated derivative" nor how to assess such.

Conclusion

11. Patent term adjustments cannot be determined until after allowable subject matter has been indicated and notice of allowance has been submitted. (See MPEP § 1.705 (a)).

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Nina Archie
Examiner
Art Unit 1645

/Robert A. Zeman/
for Nina Archie, Examiner of Art Unit 1645